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PATENT SPECIFICATION

NO DRAWINGS

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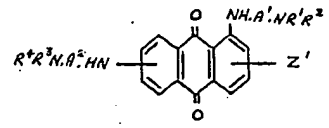
COMPLETE SPECIFICATION

Diaminoanthraquinones

THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1, a company incorporated in England, does hereby declare the invention for which they pray that a patent may be granted to them and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to chemical compounds.

It has been found that diaminoanthraquinones of formula (I) and their acid addition salts are active against infections of *Hymenolepis nana* in mice and *Oöchoristica symmetrica* in mice.



(I)

In formula (I):

$R^4R^5N.A^2.NH$—is in either position 5 or 8;

A^1 and A^2 are the same and each is a straight or branched alkylene chain containing from 2 to 12 carbon atoms;

NR^1R^2 and NR^3R^4 are the same and each is a dimethylamino, *N*-ethyl-*N*-methylamino, diethylamino, pyrrolidino, piperidino, hexamethyleneimino, morpholino, piperazino or N^1-alkylpiperazino group;

Z^1 is a hydrogen atom or an alkyl group and is in any one of positions 2, 3 or 4; and

In the definition of formula (I) and as used herein, "alkyl" denotes a saturated aliphatic hydrocarbon containing from 1 to 4 carbon atoms.

The present invention in one aspect provides the diamino-anthraquinones of formula (I) and the acid addition salts thereof.

The activity of the acid addition salts of the diaminoanthraquinones of formula (I) resides in the bases. However, the acid in the salts is preferably pharmacologically and pharmaceutically acceptable. For example, it may be hydrochloric, sulphuric, citric, lactic, succinic, oxalic or *p*-toluenesulphonic acid.

The diaminoanthraquinones of formula (I) and their acid addition salts may be prepared by any method which is known to be useful for the preparation of aminoanthraquinones. Conveniently the 1,5- and 1,8-diaminoanthraquinones are prepared by the reaction of respectively a 1-X^1-5-X^2-anthraquinone and a 1-X^1-8-X^2-anthraquinone with an ω-disubstituted-aminoalkyleneamine, where X^1 and X^2 are the same or different and each is a reactive atom or group; for example, X^1 and X^2 may each be a halogen atom, or a hydroxy or nitro group, or an alkoxy group, or a sulphonic acid group, $—SO_3Y$, wherein Y is a hydrogen atom or an alkali metal atom such as a potassium atom. The reaction is effected in the presence of an acid binding agent, for example in the presence of an excess of the ω-disubstituted-aminoalkyleneamine or in the presence of pyridine, dimethylaniline or an alkali-metal carbonate such as potassium carbonate, at an elevated temperature, for example between 60°C and 160°C and preferably between 100°C and 150°C. Further, the reaction is effected in the presence or

[*Pric*

absence of a solvent, for example water, amyl alcohol, toluene, aniline or pyridine, and of a catalyst, for example copper powder or a copper salt such as cupric acetate.

The diaminoanthraquinone of formula (I) which is prepared by the above reaction may be isolated as the base or may be converted to an acid addition salt. For example, the acid addition salt may be formed by dissolving the base in a solvent such as water, adding the desired acid and removing the solvent by evaporation or distillation. The acid addition salt which is obtained may be converted by double decomposition, for example in solution or on an ion exchange column, into the salt of another acid.

The diaminoanthraquinones of formula (I) and their acid addition salts may be presented in a pharmaceutical composition, preferably in a unit dosage form, comprising the diaminoanthraquinone of Formula (I) or one of its acid addition salts and an acceptable carrier therefor. The composition may be made by any of the methods well known to the art of pharmacy for the manufacture of pharmaceutical compositions. For example, fine powders or granules of the compound may contain diluents and dispersing and surface active agents, and may be presented in a draft or drench in water or in a syrup; in capsules or cachets in the dry state or in a non-aqueous suspension, when a suspending agent may be included; in tablets when binders and lubricants may be included; or in a suspension in water or a syrup or an oil or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may be included. The granules or the tablets may be coated. The preferred compositions are capsules and cachets.

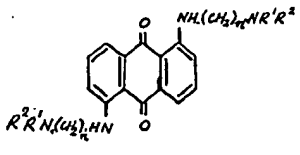
This invention will now be described with reference to the following examples in which all temperatures are given in degrees Centigrade and "m.p." is the melting point.

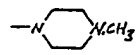
EXAMPLE 1

1,5-Dichloroanthraquinone (30 g.), 2-diethylaminoethylamine (40 ml.), anhydrous potassium carbonate (20 g.), copper powder (1.2 g.), cupric acetate (2.4 g.) and amyl alcohol (180 ml.) were mixed and boiled under reflux for 20 hours. The amyl alcohol was removed by steam distillation and the residual suspension was acidified with dilute hydrochloric acid. A small amount of undissolved solid was filtered off and the acid filtrate was made alkaline with an excess of ammonium hydroxide solution. 1,5-Bis-(2-diethylaminoethylamino)anthraquinone was filtered off as a purple-brown precipitate, and was washed with water, dried and crystallised from alcohol, depositing purple crystals with a metallic lustre, m.p. 163—165°. The dihydrobromide, prepared by adding aqueous hydrobromic acid to a hot alcoholic solution of the base, crystallised in scarlet needles, m.p. 303° with decomposition.

The 1,5-diaminoanthraquinones in Table (I) were prepared by methods analogous to those in Example 1.

TABLE (I)



Example	n	NR^1R^2	M.P.	
			Base	Dihydrochloride
2	2	$-N.(CH_3)_2$	188—190°	317° (decomposition)
3	3	$-N.(CH_3)_2$	—	287—9°
4	3	$-N.(C_2H_5)_2$	—	285—7°
5	4	$-N.(C_2H_5)_2$	—	238—240°
6	5	$-N.(C_2H_5)_2$	115°	235—6°
7	3		104—7°	283—5°
8	2		175—7°	327° (decomposition)
9	3		—	295° (Tetrahydrochloride)
10	10	$-N.(C_2H_5)_2$	—	213—215° (dihydrobromide)

EXAMPLE 11

1,5-Dichloroanthraquinone (60 g.) and 2-diethylaminoethylamine (150 ml.) were mixed and boiled under reflux for 8 hours. The excess amine was distilled off under reduced pressure and the residue was dissolved in dilute hydrochloric acid. The acid solution was made alkaline with sodium hydroxide solution and the precipitate of 1,5-bis-(2-diethylaminoethylamino)-anthraquinone was filtered off, washed with water, dried and crystallised from alcohol m.p. 163—5°. It was identical with the base in Example 1.

EXAMPLE 12

1,5-Dinitro-2-methylanthraquinone (10.4 g.), pyridine (104 ml.) and 2-diethylaminoethylamine (18.8 ml.) were mixed and boiled under reflux for 4 hours. Pyridine and excess of the amine were distilled off under reduced pressure, and residual solid was extracted with dilute hydrochloric acid, and a trace of undissolved solid was filtered off. The acid filtrate was made alkaline with sodium hydroxide solution and extracted with ether to yield 1,5-bis-(2-diethylaminoethylamino)-2-methylanthraquinone, a dark red, syrupy base. The dihydrochloride, prepared by adding aqueous hydrochloric acid to an alcoholic solution of the base, crystallised in lustrous, red needles, m.p. 260—265° with decomposition.

EXAMPLE 13

Anthraquinone-1,5-disulphonic acid sodium salt (7 g.), 3-dimethylaminopropylamine (10.5 g.), *m*-nitrobenzene sodium sulphonate (5 g.) and water (40 ml.) were

mixed and heated under pressure at 140—170° for 24 hours. 1,5-Bis-(3-dimethylamino-propylamino)-anthraquinone, which was a dark-red solid, was filtered off and washed with water. The dihydrochloride, prepared by adding aqueous hydrochloric acid to an alcoholic solution of the base, was crystallised and was identical with the product obtained from 1,5-dichloroanthraquinone (Example 3).

EXAMPLE 14

1,8-Dichloroanthraquinone (10 g.) and 3-diethylaminopropylamine (25 ml.) were refluxed for 6 hours with amyl alcohol (25 ml.) The resulting mixture was acidified and steam distilled to remove the amyl alcohol. The acid solution was made alkaline with sodium hydroxide solution and the precipitate of 1,8-bis(3-diethylamino-propyl-amino)-anthraquinone was converted into the dihydrochloride by addition of hydro-chloric acid. The salt was recrystallised from ethanol and had a m.p. 282—284°.

EXAMPLE 15

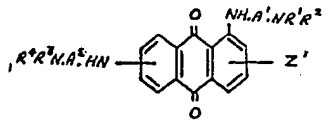
1,8-Bis(2-diethylaminoethylamino)-anthraquinone was prepared by methods analo-gous to those described in Example 14; the dihydrochloride had a m.p. of 263—265°.

EXAMPLE 16

1,5-Bis(4-diethylamino-1-methylbutylamino)-anthraquinone was prepared by methods analogous to those described in Example 14; the binoxalate had a m.p. 177—179°.

WHAT WE CLAIM IS:—

1. Diaminoanthraquinones of formula (I):



(I)

wherein $R^1R^2N.A^2.NH$— is in either position 5 or 8;

A^1 and A^2 are the same and each is a straight or branched alkylene chain containing from 2 to 12 carbon atoms;

NR^1R^2 and NR^3R^4 are the same and each is a dimethylamino, *N*-ethyl-*N*-methyl-amino, diethylamino, pyrrolidino, piperidino, hexamethyleneimino, morpholino, piper-azino or *N*-alkylpiperazino group;

Z^1 is a hydrogen atom or an alkyl group and is in any one of positions 2, 3 or 4; and

and the acid addition salts thereof.

2. A diaminoanthraquinone compound substantially as hereinbefore described in any of the foregoing examples.

R. F. HASLAM,
Agent for the Applicant,
Chartered Patent Agent.

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